Respiratory Medicine (2004) **98**, S16–S21

respiratoryMEDICINE

Tools to assess (and achieve?) long-term asthma control

Antoine Magnan*

Université de la Méditerranée, Hôpital Ste Marguerite, Marseille, France

KEYWORDS
Asthma control;
Induced sputum;
Eosinophilia;
Exhaled NO;
Bronchial hyperreactivity;
Exacerbations

Summary Assessment tools are needed to monitor asthma control and to detect exacerbations before the alteration of functional parameters and the occurrence of symptoms. The ability to effectively monitor asthma control would enable clinicians to increase corticosteroid dose or to stop corticosteroid tapering before symptoms occur. As a few severe exacerbations are expected per year in treated patients, these tools must be suitable for long-term use. They must also be reproducible, acceptable to patients and be non-invasive. Tools currently available to assess asthma control include assessment of: clinical parameters (e.g. nocturnal awakenings; bronchodilator intake; symptom scores); lung function (e.g. peak expiratory flow and forced expiratory volume in 1 s); subjective parameters of asthma control (e.g. asthma control questionnaire (ACQ)); bronchial hyper-responsiveness; eosinophilia in induced sputum; and exhaled nitric oxide (NO) concentration. Clinical symptoms, lung function and the ACQ have proved to be inadequate markers of asthma control, as changes in these parameters occur at the same time as symptom manifestation. By contrast, sputum eosinophilia and exhaled NO concentrations are truly predictive of asthma exacerbations; monitoring these parameters are useful in preventing exacerbations from occurring in the first instance. They also assess, and help to achieve asthma control in the long term.

Introduction

The symptoms of most asthmatic patients can be adequately controlled by currently available therapy, primarily inhaled corticosteroids (ICSs). However, a loss of asthma control after some months occurs in a proportion of asthmatic patients, leading to exacerbations, hospitalisation(s) and treatment with oral corticosteroids, which potentially have long-term adverse effects. With treatment, asthma control is regained, but the symptom

Abbreviations: ACD, asthma control diary; ACQ, asthma control questionnaire; AMP, adenosine monophosphate; BHR, bronchial hyper-responsiveness; BTS, British Thoracic Society; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; IS, induced sputum; LABA, long-acting β_2-agonist; NO, nitric oxide; PEF, peak expiratory flow

*Corresponding author. Tel.: +33-491-407310; fax: +33-491-741606.
E-mail address: antoine.magnan@mail.ap-hm.fr (A. Magnan).

0954-6111/$ - see front matter
doi:10.1016/j.rmed.2004.07.011

baseline becomes elevated, reflecting the airway remodelling component of asthma. In these patients, exacerbations can be triggered by allergen or pollutant exposure, tobacco smoke or infection. In many cases, non-compliance with treatment is a factor in loss of asthma control. However, in some cases, no triggering factor is found. Tapering of corticosteroid treatment in these patients is especially difficult since it represents a risk of exacerbation.

Asthma control needs to be monitored in the long-term. Long-term studies are more indicative of 'real life' situations and allow the assessment of asthma control, exacerbations and airway remodelling. In 'real life' situations patients are exposed to unscheduled triggering factors such as allergens, tobacco smoke and other pollutants, may have concomitant diseases (e.g. rhinitis, gastroeosophageal reflux) and are more than likely to be non-compliant with therapy. In a recent long-term study, Pauwels and colleagues[1] showed that in patients with mild asthma, control was achieved following treatment with inhaled budesonide. However, even these patients with mild asthma experienced an exacerbation of their disease whilst on ICS therapy.[1] Patients with severe asthma have an exacerbation several times a year. Clearly, there is an unmet clinical need in these patients to develop tools to assess the long-term control of asthma and also to predict when loss of control is about to occur, before symptoms and impaired lung function occur.

Tools to monitor asthma control

Early detection of loss of asthma control is important as it enables: (1) effective prophylactic therapy to be given before symptoms become apparent and also (2) allows the determination of the lowest effective dose of treatment. Fig. 1a shows how monitoring asthma control enables therapy to be given before symptoms present. Without a marker of asthma control patients' asthma often exacerbates and is usually treated with oral corticosteroids (treatment 2) to regain control of the disease. Once the exacerbation has subsided add-on therapy, such as a long-acting β_2-agonist (LABA), is usually initiated to maintain control (treatment 3). Using a marker which is indicative of imminent loss of asthma control enables prophylactic therapy to be initiated (treatment 1′) before symptoms manifest. Maintenance therapy can then be achieved on a lower dose. However, it is essential that the marker chosen to indicate the status of asthma control is detectable before symptoms present (Fig. 1a).

Markers of asthma control can also be used to determine the lowest efficient dose of ICSs (Fig. 1b). Once control of asthma has been achieved for 3 months (treatment 3), asthma management guidelines recommend reducing the number of add-on therapies (treatment 2) and gradually reducing the corticosteroid dose (treatment 1). Patients who re-exacerbate during steroid tapering are frequently reassigned to a therapy regimen with proven efficacy which attained control of their asthma in the past (e.g. ICSs and LABAs; treatment 3). Once control has been reachieved, add-on therapies can again be removed but steroid tapering (treatment 1) avoided. A good predictor of impending loss of asthma control would indicate that loss of control is about to occur before symptoms have become apparent during steroid tapering (Fig. 1b). In this instance a prophylactic therapy (treatment 1′) could be introduced thus avoiding the occurrence of symptoms and maintenance can be achieved on a lower dose.

Many tests to assess asthma control are now available and include assessment of clinical parameters (e.g. nocturnal awakenings, bronchodilator intake), lung function (e.g. forced expiratory volume in 1 s (FEV_1); peak expiratory flow (PEF)); subjective parameters (e.g. asthma control questionnaire (ACQ)); bronchial hyper-responsiveness (BHR); induces sputum (IS) eosinophilia; and exhaled nitric oxide (NO) concentration. The ideal test to monitor asthma control should be safe, non-invasive and reproducible. The selected marker of asthma control should be predictive of an exacerbation and occur before symptoms present.

Clinical assessment

Clinical parameters frequently used to assess asthma control include nocturnal awakenings, bronchodilator intake and symptom scores. However, these parameters do not predict loss of asthma control, as clearly if they are elevated then patients are already experiencing symptoms, a fact which was highlighted by Tattersfield and colleagues.[2] They examined change in PEF, symptoms, and use of rescue β-agonists during the 425 severe exacerbations that occurred during a 12-month parallel group study in which low and high doses of budesonide with and without formoterol were compared in patients with asthma. Results showed that reduction in PEF was a late indicator of loss of asthma control, occurring at the same time

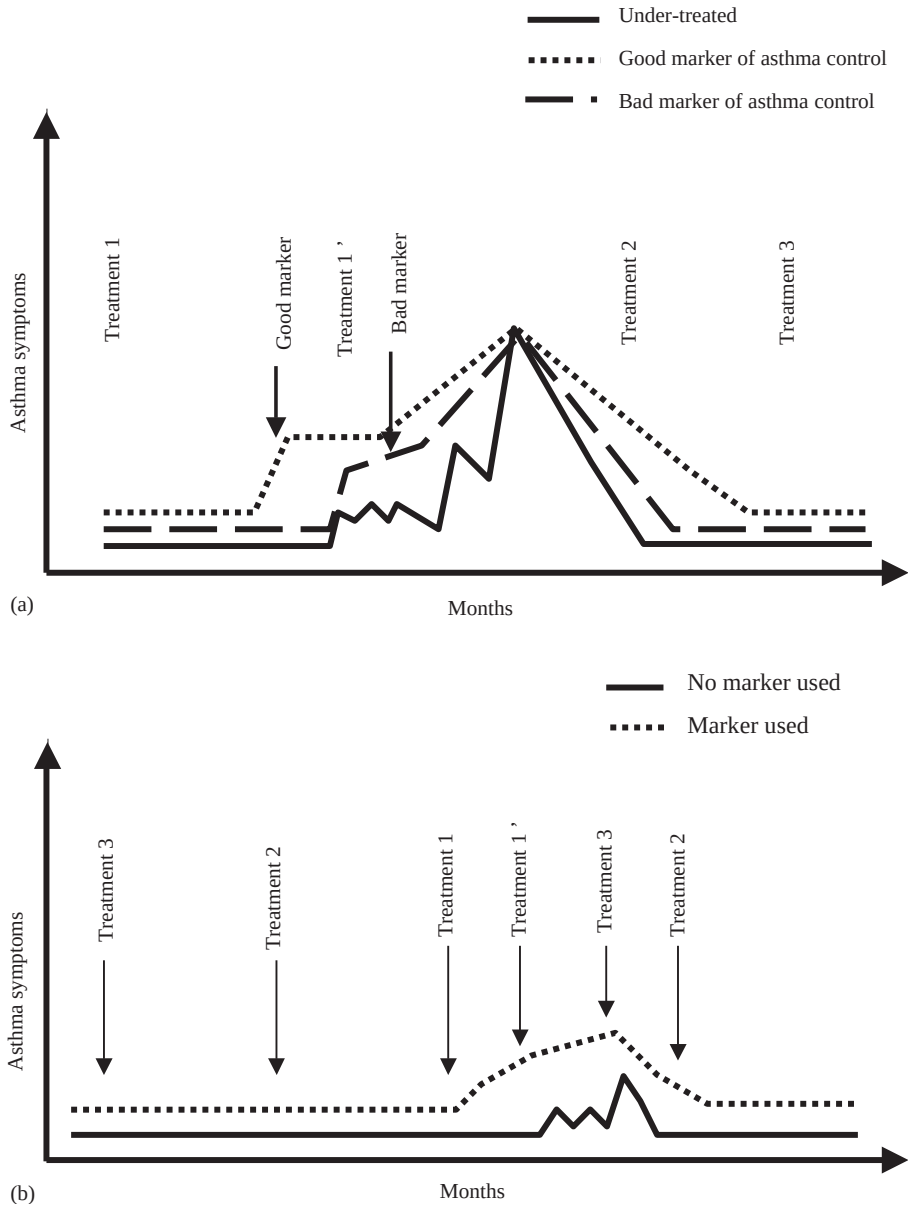

Figure 1 Schematic representation of how tools to assess loss of asthma control can (a) prevent the occurrence of exacerbations, and (b) determine the lowest effective dose of ICSs.

as symptoms.[2] Exacerbations were characterised by a gradual fall in PEF over several days, followed by more rapid changes over 2–3 days. An increase in symptoms and rescue β-agonist use occurred in parallel, and both the severity and time course of the changes were similar in all treatment groups.[2] (Fig. 2)

Similarly, reduction in FEV_1 represents an asthmatic symptom and so cannot be considered as an early indicator of exacerbation.[3,4] Pizzichini and colleagues[4] induced exacerbations by lowering the dose of ICSs in prednisolone-dependent asthmatics and showed that reduction of prednisone treatment evoked a severe airway eosinophilic inflammatory response. A drop in FEV_1 occurred 6 weeks after sputum eosinophilia was detected suggesting that sputum examination, but not FEV_1 assessment, may be useful in identifying the minimum regular dose of prednisone required in these patients.[4]

Questionnaires

Daily symptoms, PEF, and medication diaries are often used in clinical trials of treatments for asthma on the assumption that they provide a better estimate of clinical status than does a questionnaire completed in the clinic. Juniper and

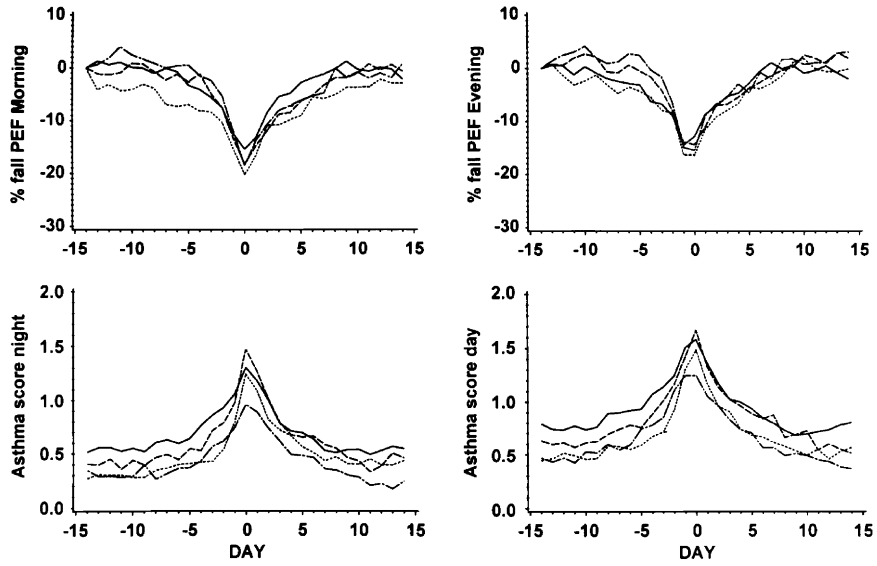

Figure 2 Drop in PEF rate occurs at the same time as occurrence of symptoms. Reprinted with permission from Tattersfield et al.[2]

colleagues[5] conducted a study comparing the measurement properties of the clinic-completed ACQ with those of the Asthma Control Diary (ACD) in 50 adults with symptomatic asthma. The diary is composed of questions and response options which are almost identical to those of the ACQ, but uses PEF instead of FEV_1 as the measure of airway caliber. Results showed high concordance between the questionnaire and diary, but both responsiveness and reliability were better with the ACQ. Both the ACQ and the ACD were valid instruments for measuring asthma control, but the questionnaire had slightly better discriminative and evaluative measurement properties than does the diary.[5] However, in terms of predictive power, both the ACQ and the ACD are late indicators of loss of asthma control reflecting the occurrence of symptoms rather than their imminent arrival.

Bronchial hyper-responsiveness

Non-specific BHR decreases when asthma is controlled and increases before an exacerbation of asthma. Jatakanon and colleagues[6] showed that BHR decreased following treatment with budesonide (100–1600 μg) in a dose-responsive manner in mild stable steroid naïve asthmatic patients. There were also significant improvements in FEV_1 following 400 and 1600 μg budesonide which was accompanied by significant reductions in eosinophil numbers in induced sputum (IS). Concentrations of exhaled NO were reduced following each budesonide dose, while BHR was improved only with 1600 μg budesonide.[6] However, the procedure used to measure BHR can in itself produce symptoms of asthma and so results are difficult to interpret. In addition, BHR and exhaled NO may not reflect the control of airway inflammation as accurately as the number of eosinophils in sputum.

Sont and colleagues[7] used measurement of BHR to assess control in stable asthmatic patients (n=75) whilst tapering ICS dose. One group was treated with ICSs based on the results of BHR and the other group treated according to asthma management guidelines. Patients treated according to the BHR strategy had a 1.8-fold lower rate of mild exacerbations than did patients in the reference strategy group and exhibited a clinically significant improvement of 200 ml in their FEV_1 (Fig. 3a).[7] However, the dose of ICSs in the BHR group was twice that observed in the reference strategy group (Fig. 3b) indicating that monitoring BHR may reduce the threshold of ICS increase, leading to over-treatment in some patients. In a crossover study in patients with mild-to-moderate asthma BHR to adenosine monophosphate (AMP) was an early and sensitive indicator of the beneficial anti-inflammatory effect of budesonide.[8] A significant change of 1.6 ± 0.3, 2.2 ± 0.3, and 2.8 ± 0.3 doubling doses of PC(20) AMP was observed at 1, 4, and 6 weeks, respectively, in the course of budesonide treatment.[8]

Eosinophilia and exhaled nitric oxide

Treatment decisions in asthma are usually based on assessments of symptoms and simple measures of lung function, which do not relate closely to

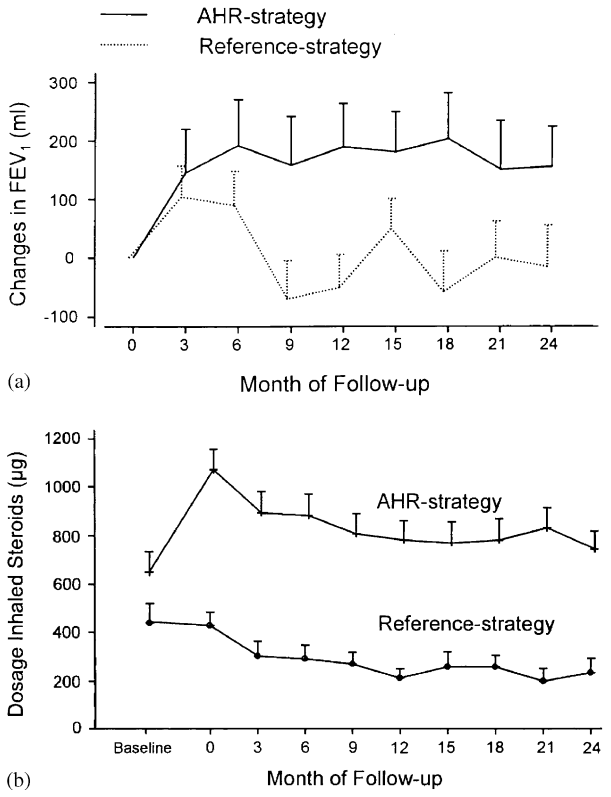

Figure 3 Using airway hyper-responsiveness (AHR) instead of asthma management guidelines to monitor asthma control in stable asthmatic patients results in (a) lower incidence of exacerbations as assessed by drop in FEV_1 but, (b) higher dose of ICSs. Reprinted with permission from Sont et al.[7]

underlying eosinophilic airway inflammation. Counting the number of eosinophils in IS has been used to monitor the adjustment of therapy in asthmatics.[9] Monitoring IS eosinophil counts allows an inflammatory diagnosis which specifically monitors ICS use. Indeed, the persistence of a significant bronchial eosinophilia in treated patients reflects insufficiency of ICS treatment, and/or poor compliance with the treatment regimen.[10] However, IS is a time-consuming procedure and is not applicable to all patients.

An alternative approach is to use a surrogate marker of eosinophilia. Exhaled NO reflects the eosinophilic inflammation in asthma and is easy to monitor,[11] but is probably less specific than counting eosinophils directly. Although the evidence to support the routine use of measurement of exhaled NO in the management of patients with asthma is limited, it may prove to be useful in assessing adherence to treatment with ICSs, or in the identification of patients in whom respiratory symptoms are associated with eosinophilic airway inflammation. In a study by Jatakanon and colleagues,[3] the dose of ICSs was reduced to 200 µg in an attempt to induce an exacerbation in patients with stable asthma (n=15). NO, methacholine challenge and eosinophils in sputum were measured twice a week for 8 weeks in these patients. At the end of the study seven patients had developed an exacerbation and eight had not. Baseline exhaled NO did not predict exacerbation risk (Fig. 4). The only significant difference between the two groups at baseline was a higher baseline sputum eosinophil count in subjects with subsequent exacerbations (Fig. 5), and this elevation was noted before any functional alterations accompanying exacerbations occurred.[3] The increases in sputum eosinophils and exhaled NO were correlated with decreases in airway function, including decreases in morning PEF and FEV_1.[3] Multiple regression analysis suggested that the change in sputum eosinophils is a potentially useful marker in predicting loss of asthma control reflected by loss of airway function.

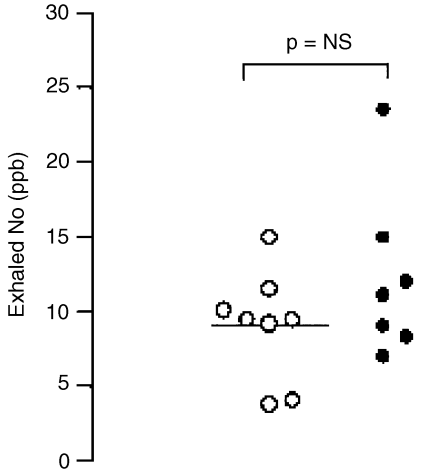

Figure 4 Concentration of exhaled NO at baseline is not a good marker of exacerbation risk. Reprinted with permission from Jatakanon et al.[3]

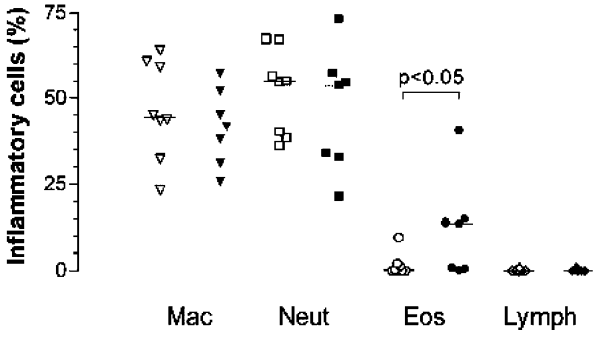

Figure 5 Number of eosinophils in IS is a good marker of exacerbation risk. Mac: macrophages; Neut: neutrophils; Eos: eosinophils; Lymph: lymphocytes. Reprinted with permission from Jatakanon et al.[3]

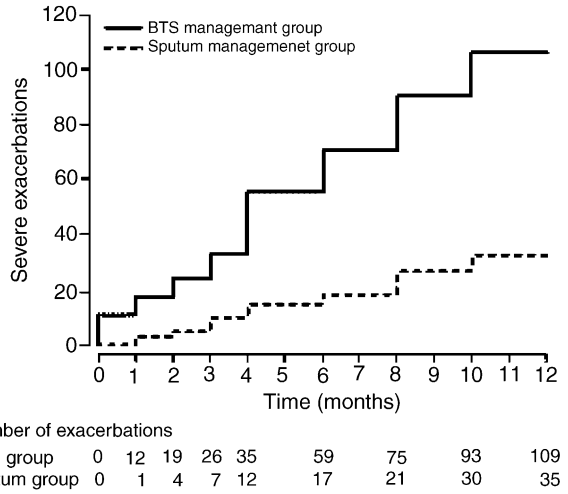

Figure 6 Patients treated according to sputum eosinophilia experience fewer exacerbations than patients treated according to BTS guidelines. Reprinted with permission from Green et al.[9]

Green and colleagues[9] assessed whether a management strategy that minimised eosinophilic inflammation reduced asthma exacerbations compared with a standard management strategy. Seventy-four patients with moderate-to-severe asthma were randomly allocated to management either by standard British Thoracic Society asthma guidelines (BTS management group) or by normalisation of IS eosinophil count and reduction of symptoms (sputum management group). The sputum eosinophil count, incidence of severe exacerbations and admittance to hospital were all significantly reduced over 12 months in the sputum management group than in the BTS management group (Fig. 6).[9] They also showed that FEV_1 and other functional parameters were not different between the two groups clearly indicating that variation in FEV_1 cannot be used as a marker for potential exacerbation.[9] Contrary to the findings by Sont and colleagues[7] who used BHR results as their treatment guide, the average daily dose of inhaled or oral corticosteroids did not differ between the two groups.[9] Taken together, these considerations indicate that assessment of asthma control in the long-term in asthmatics with repeated exacerbations should include several complementary methods including IS, especially with regard to ICS use.

Conclusions

To date IS eosinophilia is the best-validated tool predictive of loss of asthma control. However, IS is a time-consuming procedure and so other procedures are needed for routine use. Increased bronchial responsiveness to methacholine is also predictive of loss of asthma control, but the procedure used to measure it is very invasive and can itself produce symptoms of asthma. Additionally, monitoring asthma control as a function of BHR may result in over-treatment with ICS. These procedures are certainly useful in preventing exacerbations. They assess, and help to achieve asthma control in the long-term. The ACQ may be considered, but most likely changes in the questionnaire would be observed when loss of asthma control has already occurred and patients are experiencing symptoms. Exhaled NO is a promising surrogate marker of asthma control although studies are needed to assess its applicability in the long-term assessment of asthma. Other applications of these predictive tools should be considered and include assessment of compliance and prediction of ICS efficiency in patients with asthma.

References

1. Pauwels R, Pedersen S, Busse W, et al. Early intervention with budesonide in mild persistent asthma, a randomised, double-blind trial. *Lancet* 2003;**361**:1066–7.
2. Tattersfield A, Postma D, Barnes P, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. *Am J Respir Crit Care Med* 1999;**160**:594–9.
3. Jatakanon A, Lim S, Barnes P. Changes in sputum eosinophils predict loss of asthma control. *Am J Respir Crit Care Med* 2000;**161**:64–72.
4. Pizzichini M, Pizzichini E, Lelland L, et al. Prednisone-dependent asthma: inflammatory indices in induced sputum. *Eur Respir J* 1999;**13**:5–7.
5. Juniper E, O'Byrne P, Ferrie P, King D, Roberts J. Measuring asthma control. Clinic questionnaire or daily diary. *Am J Respir Crit Care Med* 2000;**162**:1330–4.
6. Jatakanon A, Kharitonov S, Lim S, Barnes P. Effect of differing doses of budesonide on markers of airway inflammation in patients with mild asthma. *Thorax* 1999;**54**:108–14.
7. Sont J, Willems L, Bel E, et al. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment, The AMPUL Study Group. *Am J Respir Crit Care Med* 1999;**159**:1043–51.
8. Prosperini G, Rajakulasingam K, Cacciola R, et al. Changes in sputum counts and airway hyperresponsiveness after budesonide: monitoring anti-inflammatory response on the basis of surrogate markers of airway inflammation. *J Allergy Clin Immunol* 2002;**110**:855–61.
9. Green R, Brightling C, Mckenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;**360**:1715–21.
10. Parameswaran K, Leigh R, Hargreave F. Sputum eosinophil count to assess compliance with corticosteroid therapy in asthma. *J Allergy Clin Immunol* 1999;**104**:502–3.
11. Payne D. Nitric oxide in allergic airway inflammation. *Curr Opin Allergy Clin Immunol* 2003;**3**:133–7.